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Diurnal changes of critical flicker frequency in patients with liver cirrhosis and their relationship with sleep disturbances

Genco Gencdal*, Fulya Gunsar, Cenk Emre Meral, Esin Salman, Berna Gürsel, Nevin Oruç, Zeki Karasu, Galip Ersoz, Ulus S. Akarca

Ege University School of Medicine, Department of Gastroenterology, Izmir, Turkey

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ABSTRACT

Background: We aimed to measure the diurnal changes of critical flicker frequency in healthy subjects and cirrhotic patients and to investigate their relationship with sleep disturbance.
Methods: Cirrhotic patients and healthy volunteers were included. All groups completed the Pittsburgh Sleep Quality Index and a simple sleep questionnaire. Sleep disturbance was defined as a Pittsburgh Sleep Quality Index score of >5. Critical flicker frequency was measured twice a day to detect diurnal abnormalities.
Results: Overall, 59 cirrhotic patients (54.2% males, Mean Age 59 ± 11 years) and 18 controls (39.9% males, Mean Age 58 ± 9 years) were included. Sleep disturbances were more common in cirrhotics (66.1%) than controls (38.9%, $p < 0.05$). In cirrhotics, the critical flicker frequency was not related to decompensation. The nocturnal values were higher than the morning values in cirrhotics (64.4%), but not in controls ($p < 0.0001$). Additionally, sleep disturbances were more common in cirrhotics who had higher nocturnal values ($p < 0.05$).
Conclusions: Changes in the diurnal critical flicker frequency were observed in cirrhotics but not in controls. Sleep disturbances in cirrhotics appear to be associated with deviations of the diurnal rhythm of critical flicker frequency rather than with clinical parameters such as the clinical stages of cirrhosis and the Model For End-Stage Liver Disease and Child–Pugh scores.

1. Introduction

Approximately two-thirds of cirrhotic patients suffer from sleep disturbances, which may manifest as being more alert at night than in the morning. Although the reason for these sleep disturbances remains unclear it may be related to minimal hepatic encephalopathy (MHE), which is acknowledged as an early phase of hepatic encephalopathy (HE) [1].

MHE is neither a completely standardized condition nor has a clear clinical significance and detection criteria. As most of the tests to detect MHE depend on the ability of the patient, it is very difficult to standardize them. Therefore, objective tests that do not have interpersonal variability and that can be easily applied are needed. The critical flicker frequency (CFF) measures patient wakefulness and can be used to detect MHE. Being an objective and easily implemented test, CFF is becoming more widely used to detect MHE [2–4]. It is assumed that retinal gliopathy is indicative of cerebral gliopathy in patients with hepatic encephalopathy and CFF is a visual test that is sensitive to such changes in retinal glial cells [4]. Given the advantages of language independence, and being simple to perform and interpret, CFF is suggested for use for detecting MHE rather than psychometric and neurophysiologic tests [5–7]. However, recent data and a meta-analysis showed that CFF has a high specificity and moderate sensitivity for diagnosing minimal hepatic encephalopathy, therefore suggesting that the use of CFF could be an adjunct to psychometric testing [8,9].

We hypothesized that abnormal CFF, as the indicator of MHE, could be associated with sleep disturbances. Therefore, we aimed to investigate the morning to night changes of CFF in cirrhotic patients and healthy subjects, as well as the relationship of these changes and CFF with sleep disturbances.

* Corresponding author at: Ege Üniversitesi Tıp Fakültesi Hastanesi, Namık Kemal Menteş, Gastroenteroloji Kliniği, 35040, Bornova, İzmir, Turkey.
Tel.: +90 0232 3904397/5063581760; fax: +90 232 3745761.
E-mail addresses: gencogencdal@yahoo.co.uk, gencogencdal@gmail.com (G. Gencdal).

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2. Patients and methods

2.1. Patient selection

Patients with liver cirrhosis (18–70 years of age) who were admitted to our outpatient clinic between August 2011 and May 2012 were included in the study. Written informed consent was obtained from all participants before enrolment. Patients with a history of overt HE were required to be free from HE findings during the preceding 6 months according to notes of our outpatient clinic and their medical history. Patients with alcoholic cirrhosis were excluded if they were not abstinent for at least 6 months, and patients taking sedatives, hypnotics, selective serotonin reuptake inhibitors, and neuroleptics were excluded. The diagnosis of cirrhosis was based on clinical, biochemical, endoscopic, and radiological findings, while liver biopsies were performed when necessary. The severity of liver disease was assessed using the Child's Pugh grading system and MELD scores. Twenty-two patients who were taking lactulose, L-ornithine, L-aspartate, or antibiotics stopped these medications at least one week prior to testing to avoid affecting the results.

Patients were also classified as decompensated if they had any of the following conditions: ascites, history of hepatic encephalopathy, variceal bleeding, bilirubin level >3 mg/dl in non-biliary cirrhosis (>6 mg/dl in biliary cirrhosis), or INR > 1.9.

Age-matched healthy volunteers were included in the study as the control group. None of the controls had chronic liver or neuropsychiatric disease or abused alcohol. In addition, none of the controls was taking medications known to affect sleep.

2.2. Measurement of sleep disturbances

All patients and controls completed a validated Turkish Form of the Pittsburgh Sleep Quality Index (PSQI) [10,11] and a simple sleep questionnaire (STSQS) [12].

The total PSQI score is between 0 and 21. This validated tool is used to assess sleep quality and sleep disturbances over the preceding month. The questionnaire contains 19 questions that are used to generate seven components, each of which is scored from zero to three, where three represents the negative extreme. These component scores are then summed to provide the total PSQI score (range: 0–21). The PSQI testing takes approximately 10 min to complete and 5 min to score [10].

The STSQS, which was described by Montagnese et al., provides a simple overall assessment of sleep quality rated on a 1–9 analogue scale (1 = best, 9 = worst sleep ever) and allows for the collection of information on habitual sleeping parameters such as bedtime, total sleep time, sleep latency, night awakenings, and waking and arousal times during the preceding month [12]. The STSQS takes 1–2 min to complete without additional time for scoring.

Sleep disturbance was defined as a PSQI score (0–21) of >5 or an STSQS score ≥4.

2.3. Measurement of the critical flicker frequency threshold

The CFF was measured with an HEPAtonorm analyzer (HE-Flicker Diagnostics, Germany). The patients were first trained and instructed on the procedure. By decreasing the frequency of the light pulses from 60 Hz downward, the CFF threshold was determined as the frequency at which the impression of fused light turned to a flickering one. Flicker frequencies were measured 9 times for each measurement, and the mean value was calculated. Measurements below 38.9 Hz were designated as abnormal CFF, based on the CFF results obtained from our unpublished previous study, which is consistent with a German study [13]. The cut-off was calculated as 2 standard deviations below the mean CFF values found in healthy volunteers. The CFF was measured twice a day (at 10 am and at 10 pm) for all cirrhotic patients and controls. The measurements performed at 10 am and 10 pm were defined morning measurement (CFFam) and night measurement (CFFpm), respectively. We then evaluated the differences between CFFam and CFFpm.

The ethics committee approval was received on August 1, 2011 (Registration Number: 11-5/7).

Table 1
Clinical characteristics of 59 cirrhotic patients.

Age	58.8 ± 11.4
Male gender	32 (54.2%)
Time since diagnosis in years (median)	5.95 ± 5.49 (4.0)
Aetiology	
Hepatitis B	24 (40.7%)
Hepatitis C	6 (10.2%)
Alcohol	10 (16.9%)
Other	19 (32.2%)
History of hepatic encephalopathy	8 (13.6%)
Esophageal varices	36 (61%)
Ascites	35 (59.3%)
Child–Pugh class	
A	23 (39.0%)
B	19 (32.2%)
C	17 (28.8%)
Decompensation	38 (64.4%)
Child's–Pugh score	7.7 ± 2.1
MELD score	12.2 ± 4.1

MELD: Model For End-Stage Liver Disease.

2.4. Statistics

The differences between CFFam and CFFpm in compensated and decompensated cirrhotic patients and in healthy volunteers were compared using a general linear repeated-measures model.

Since the number of healthy controls was low, the Mann–Whitney *U* test was used to compare the parametric values between controls and cirrhotic patients.

The possible differences among the nominal data were examined using the chi square test and Fisher's exact test. The Fisher's exact test was applied if the number of samples in any category was ≤5. Otherwise, the chi square test was applied.

The Wilcoxon signed rank test was used to compare the morning and night CFF values of cirrhotic patients and healthy controls.

The patients were also separately analyzed and defined as compensated or decompensated according to the presence of jaundice, ascites, variceal bleeding, and history of HE.

3. Results

Fifty-nine cirrhotic patients (54.2% males, Mean Age: 58 ± 11.4 years) and 18 healthy controls (38.9% males, Mean Age: 57.7 ± 9.2 years) were included in the study. The clinical characteristics of cirrhotic patients are shown in Table 1. Twenty four had hepatitis B virus-related cirrhosis (40.8%) and only 8 had a history of overt HE (13.5%). Thirty eight patients (64.4%) had decompensated cirrhosis and of these 35 had ascites (59.3%). Seventeen patients were in Child–Pugh class C (28.8%), the mean MELD score was 12.2 ± 4.1, and MELD score was ≥15 in 13 patients (22%).

Overall, 22 patients (37%) were receiving anti-HE treatment (lactulose, rifaximine or LOLA) until one week before CFF testing. Fourteen of the 22 patients without history of overt HE were taking these drugs due to forgetfulness or difficulties in concentration, particularly for their business. However, there were no differences in the CFFam or CFFpm measurements between those who did and did not receive anti-HE treatments (data not shown).

Table 2
Characteristics of compensated and decompensated cirrhotic patients.

	Compensated ($n=21$)	Decompensated ($n=38$)	p
Gender (male)	42.4%	55.3%	0.832
Age	58.6 ± 13.2	59.0 ± 10.4	0.905
PSQI score	7.1 ± 3.7	7.7 ± 4.2	0.535
STSQS score	5.4 ± 2.2	5.5 ± 2.2	0.815
PSQI-Sleep disturbance exists	13 (61.9%)	26 (68.4%)	0.613
STSQS-Sleep disturbance exists	13 (61.9%)	24 (63.2%)	0.924
Sleep latency (time to fall a sleep) (median)	30	30	0.289
Total sleeping time	6.4 ± 1.8	5.8 ± 1.6	0.167
CFFam	38.1 ± 4.2	38.3 ± 3.6	0.843
CFFpm	39.1 ± 4.0	38.8 ± 3.9	0.764
CFFpm and CFFam difference (median)	0.97 ± 3.27 (1.00)	0.42 ± 4.00 (0.65)	0.624
CFFam disturbance	14 (66.7%)	23 (60.5%)	0.641
CFFpm disturbance	9 (42.9%)	20 (52.6%)	0.472
Both CFF (CFFam and CFFpm) disturbance	7 (33.3%)	16 (42.1%)	0.508
Only CFFpm disturbance (CFFam is normal)	2 (9.5%)	4 (10.5%)	1.000[a]
CFFpm > CFFam	14 (66.7%)	24 (62.2%)	0.788

PSQI: Pittsburgh Sleep Quality Index; STSQS: simple sleep questionnaire; CFFam: critical flicker frequency morning; CFFpm: critical flicker frequency night.
[a] Fisher exact test.

Initially, compensated and decompensated cirrhotic patients were analyzed in terms of CFFam and CFFpm values and sleep disturbances (Table 2). According to PSQI, sleep disturbances exist in 61.9% of compensated and 68.4% of decompensated patients. The CFFam and CFFpm means were 38.1 ± 4.2 and 39.1 ± 4.0, respectively, in compensated patients, and were 38.3 ± 3.6 and 38.8 ± 3.9, respectively, in decompensated patients. The difference between CFFpm and CFFam was 0.97 ± 3.27 in compensated patients and 0.42 ± 4.0 in decompensated patients ($p > 0.05$). As there were no differences in parameters related to CFF and sleep disturbances, all cirrhotic patients were pooled for comparisons with healthy volunteers.

The comparable characteristics of cirrhotic patients and healthy controls are reported in Table 3. Cirrhotic patients and healthy controls were matched for age (58.8 ± 11.4 years, 57.7 ± 9.2 years; $p > 0.05$) and gender. The PSQI and STSQS scores were found to be higher in patients with cirrhosis than healthy controls (7.5 ± 4.0 versus 4.2 ± 2.9 and 5.4 ± 2.8 versus 3.5 ± 1.8, respectively; $p < 0.05$). Also, higher rates of sleep disturbances were observed in cirrhotic patients than healthy controls ($n = 39$, 66.1%). Sleep latency (time to fall asleep) was significantly longer in patients with cirrhosis (30 min versus 7.5 min in healthy controls), although the total sleep time was shorter in the patients with cirrhosis than healthy controls (6.0 ± 1.7 h versus 7.0 ± 1.9 h; $p < 0.05$).

The CFF measurements are shown in Table 3. Among healthy controls, the CFFam values were significantly higher than the CFFpm values (40.5 ± 2.5 versus 38.0 ± 3.1; $p < 0.0001$), indicating a diurnal CFF rhythm in healthy subjects. The diurnal CFF rhythm observed in healthy controls disappeared in cirrhotic patients: in the latter group, the CFF values did not differ between morning and night (38.3 ± 3.8, 38.9 ± 3.9; $p > 0.05$). Accordingly, the CFFam values were lower in cirrhotic patients than healthy controls (38.3 ± 3.8, 40.5 ± 2.5; $p < 0.05$), but the night values were not statistically different (38.9 ± 3.9, 38.0 ± 3.1; $p > 0.05$).

The differences between the CFF values obtained in the morning and at night are shown in Fig. 1. A significant difference was found between cirrhotic patients and healthy volunteers with respect to the changes in morning and night measurements (general linear repeated-measures model, $p = 0.001$).

The CFFpm values were higher than the CFFam values in 64.4% of cirrhotic patients; however, none of the healthy controls had higher CFFpm than CFFam values. Diurnal naps could also cause these CFF values, but we could not find any relationship between the frequency of diurnal naps and CFF. This result not only indicates that

Table 3
Characteristics of cirrhotic patients and healthy controls.

	Patients ($n=59$)	Controls ($n=18$)	p
Male gender	54.2%	39.9%	>0.05
Mean Age (years)	58.8 ± 11.4	57.7 ± 9.2	>0.05
PSQI score	7.5 ± 4.0	4.2 ± 2.9	0.002[*]
Mean STSQS score	5.4 ± 2.8	3.5 ± 1.8	0.001[*]
Sleep disturbance with PSQI	39 (66.1%)	7 (38.9%)	0.039[**]
Sleep disturbance with STSQS	32 (62.7%)	3 (16.7%)	0.001[***]
Time to fall asleep (in minutes) (median)	30	7.5	0.003[*]
Total sleeping time	6.0 ± 1.7	7.0 ± 1.9	0.02[*]
Mean CFFam	38.3 ± 3.8[a]	40.5 ± 2.5[b]	0.018[*]
Mean CFFpm	38.9 ± 3.9[a]	38.0 ± 3.1[b]	0.389[*]
Mean Difference between CFFpm and CFFam (median)	0.62 ± 3.74 (0.7)	−2.57 ± 2.99 (−1.3)	<0.0001[*]
CFFam disturbance	37 (62.7%)	6 (33.3%)	0.028[**]
CFFpm disturbance	29 (49.2%)	10 (55.6%)	>0.05
CFF both am and pm disturbance	23 (39%)	6 (33.3%)	>0.05
CFF only pm disturbance (CFFam is normal)	6 (10.2%)	4 (22.2%)	>0.05
CFFpm > CFFam	38 (64.4%)	0 (0%)	<0.0001[***]

PSQI: Pittsburgh Sleep Quality Index; STSQS: simple sleep questionnaire; CFFam: critical flicker frequency morning; CFFpm: critical flicker frequency night.
[*] Mann–Whitney U test.
[**] CS: chi square.
[***] FE: Fisher exact test.
[a] $p > 0.05$.
[b] $p < 0.0001$.

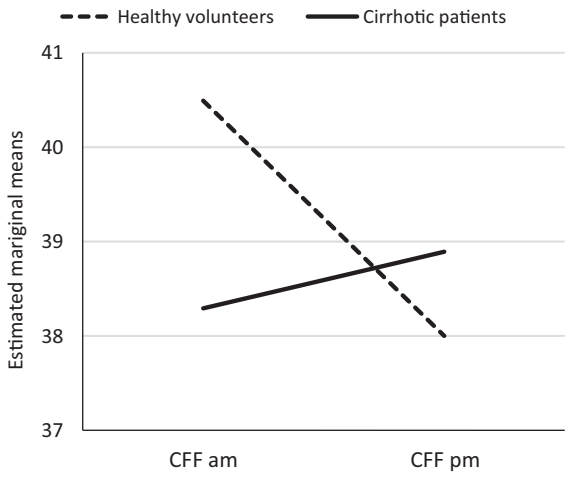

Fig. 1. Differences between critical flicker frequency morning and critical flicker frequency night values in cirrhotic patients and healthy volunteers ($p < 0.05$). *CFF: critical flicker frequency; CFFam: morning critical flicker frequency; CFFpm: night critical flicker frequency.

cirrhotic patients were more alert at night than healthy controls, but may also explain the sleep disturbances observed in patients.

The rate of sleep disturbances, as measured by the STSQS score, was 50% in those cirrhotic patients presenting CFFpm > CFFam and was 14.3% in patients with CFFpm ≤ CFFam ($p = 0.005$). Furthermore, we found a relationship, albeit a weak one, between higher CFFpm values and the presence of sleep disturbances, as determined by the PSQI scores. The rate of sleep disturbances, as measured by the PSQI score, was 81% in patients presenting CFFpm > CFFam, and was 58% in those patients with CFFpm ≤ CFFam ($p = 0.048$). Sleep timing had no relation with CFFam, CFFpm, or CFFam/CFFpm variations. Bedtime had a positive correlation with CFFpm ($r = 0.381$, $p = 0.003$): the patients with better CFF (who were more awake) went to sleep later.

No relationship was found between the difference of CFFam and CFFpm values and the Child–Pugh category, Child–Pugh score, MELD score, or gender. However, we found a relationship between the changes in morning and night CFF values and the presence of sleep disturbances, as measured by the PSQI and STSQS scores.

4. Discussion

The CFF measures patient wakefulness and can be used to detect MHE. MHE is considered to be related to sleep disturbances, which are frequently observed in conjunction with liver cirrhosis. However, there is no detailed data on whether the occurrence of MHE changes during the day is related to sleep disturbances in cirrhotic patients. In this study, we used the CFF to assess whether MHE and its diurnal changes are related to sleep disturbances in cirrhotics.

In this study, sleep disturbances were more common in cirrhotics than controls (66.1% versus 38.9%, $p < 0.05$). The CFFpm was higher than the CFFam in 64.4% of cirrhotics, meaning that 64.4% of cirrhotics were more alert at night than in the morning; however, none of the subjects had a higher CFFpm than the CFFam of the respective control ($p < 0.0001$). We also found that sleep disturbances were more common in cirrhotic patients who had a CFFpm higher than the CFFam ($p < 0.05$).

As sleep disturbances and CFF changes were expected to be more common in decompensated than in compensated patients, we initially classified cirrhotic patients into compensated cirrhosis and decompensated cirrhosis subgroups. However, these two subgroups had the same characteristics in terms of age, gender, CFF score, and sleep disturbances (probably due to the smaller number of patients). Therefore, they were pooled into one group for comparison with healthy controls.

As we confirmed in this study, sleep disturbances are frequently found in cirrhotic patients [1,12,14,15]. Up to 50–65% of patients with cirrhosis exhibit interrupted night sleep, delayed sleep habits and excessive daytime sleepiness. Cordoba et al. studied sleep quality in 44 cirrhotic patients and found that 47% of them suffered from poor sleep quality [1]. Later, similar studies in cirrhotic patients found a higher frequency of sleep disturbances compared to the healthy population [15,16]. Montagnese et al. found that cirrhotic patients took longer to fall asleep at night and wake up in the morning than healthy controls [14]. Also, in our study, sleep latency (time to fall asleep) was significantly longer in patients with cirrhosis than controls, although the total sleep time was found to be shorter in patients than controls.

In this study, in addition to the PSQI, all patients also completed a simple and practical questionnaire (STSQS) that was previously tested by Montagnese et al. [12]. Although the comparison of these two questionnaires was not the goal of this study, we found that sleep disturbances measured with the STSQS were more closely related with liver cirrhosis than were those measured with PSQI. The STSQS appears to be a rather important questionnaire as we have found it to be a practical method to detect sleep disturbances in our previous study [17].

Most studies in the literature found sleep disturbances in cirrhotic patients, but the specific mechanisms causing these disturbances remain obscure. Sleep problems in cirrhosis have generally been attributed to disease complications (e.g., ascites and pruritus), hepatic encephalopathy, or impaired hepatic melatonin metabolism [14]. Steindl et al. noted that disruption of the diurnal rhythm of melatonin may reflect alterations of the circadian function, which could contribute to the disturbances of the sleep-wake cycle that are frequently observed in patients with cirrhosis [18]. Montagnese et al. studied circadian rhythms and sleep disturbances, but the authors could not find any association between the circadian abnormalities of plasma melatonin profiles and the impaired sleep quality in a small group of patients with cirrhosis [19]. Some studies relate sleep disturbances with MHE [20–23]; however, the present study is the first to actually demonstrate a diurnal change in the CFF, an indicator of MHE, and its relationship to sleep disturbances.

In this study, we found that sleep quality in cirrhotic patients was poor and that sleep disorders were more common in these patients than healthy controls. The CFFam value was lower in patients than in healthy controls, and controls had lower CFFpm than CFFam values, but this decrease was not observed in cirrhotic patients. Therefore, while healthy controls showed wakefulness and CFF diurnal rhythm, the CFF diurnal rhythm disappeared in cirrhotic patients, since no difference was found between their CFFam and CFFpm values. None of the healthy controls was found to have a CFFpm value higher than the CFFam value; however, 64.4% of the cirrhotic patients presented higher CFFpm than CFFam values. Accordingly, a statistically significant difference was found between healthy controls and cirrhotic patients in terms of the variations between night and morning CFF values. In cirrhotic patients, the disturbances in the diurnal rhythm wakefulness were easily related to the observed sleep disturbances. While this observation may explain the sleep disturbances in cirrhotics, the causes of these changes still need to be explained. Despite diurnal naps could cause higher CFFpm values, we could not find any relationship between the frequency of diurnal naps and the CFF values.

We found no substantial relationship between the Child–Pugh score, Child–Pugh class, MELD score, albumin levels, INR, thrombocyte count, and CFF values and the changes between morning and night CFF values. Although this lack of correlation is hard to

explain, MHE can be thought of as a very early complication of liver cirrhosis.

A weakness of this study is that we used only CFF as an indicator of MHE. During the performance of this study, after the ethics committee approval in 2011, CFF has been suggested for use when detecting MHE rather than the psychometric and neurophysiologic tests [5–7]; however, some recent data and meta-analysis showed that CFF has a high specificity and moderate sensitivity for diagnosing MHE [8,9]. Therefore, CFF is now recommended for use together with psychometric or neurophysiologic tests. If we had used these tests together with CFF, the results of our study could have been more meaningful; however, as CFF is objective and simple to measure, we believe this study is still important since it shows the relationship between the diurnal changes and sleep disturbances in cirrhotics.

In conclusion, we found that the CFFam values were lower in cirrhotic patients than healthy controls. The lower CFFpm values that we observed in the healthy controls were not found in the patients. In addition, we found a strong relationship between the disruptions of the diurnal rhythm of CFF and sleep disturbances in cirrhotics. However, there was no relationship between the CFF values, or sleep disturbances, and the parameters indicating the clinical severity of the liver disease. Further investigations are required to elucidate the main reason underlying the diurnal rhythm changes in cirrhotic patients. Finally, it should be noted that the snapshot measurement of the CFF may not be indicative of MHE, while diurnal changes are likely more meaningful.

Conflict of interest

None declared.

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